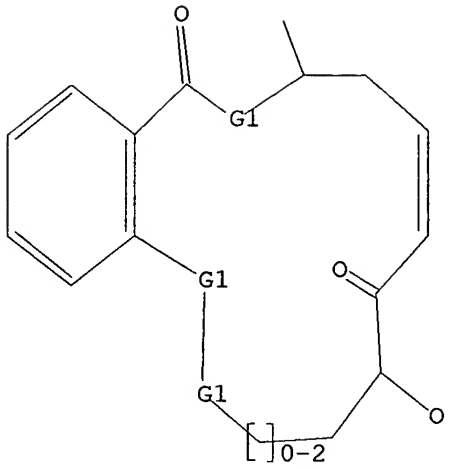
1/23/2005

STR



G1 C,O,N,S

Structure attributes must be viewed using STN Express query preparation.

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=> s l1 sss full
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FULL SCREEN SEARCH COMPLETED - 477577 TO ITERATE

 83.8% PROCESSED  400000 ITERATIONS                          19 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.06

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       477577 TO   477577
PROJECTED ANSWERS:              19 TO       36

L2            19 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               161.33     161.54

FILE 'CAPLUS' ENTERED AT 17:48:11 ON 23 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 23 Jan 2005  VOL 142 ISS 5
FILE LAST UPDATED: 21 Jan 2005  (20050121/ED)
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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l2
L3 19 L2

=> d l3 1-19 ibib abs hitstr

L3 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1038674 CAPLUS
DOCUMENT NUMBER: 142:11671
TITLE: Methods and compositions comprising an ubiquitin activator for inhibiting narrowing in mammalian vascular pathways
INVENTOR(S): Tremble, Patrice
PATENT ASSIGNEE(S): Medtronic Vascular, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004243224	A1	20041202	US 2004-818786		20040405
PRIORITY APPLN. INFO.:			US 2003-460366P	P	20030403

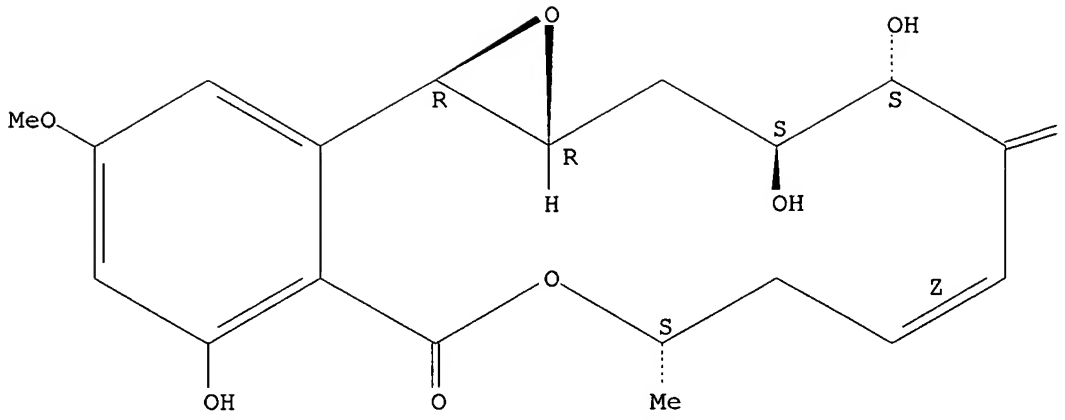
AB Methods and related compns. for treating vascular occlusions and preventing vascular narrowing are disclosed. In one embodiment an implantable medical device is provided with a coating comprising at least one cell growth inhibiting ubiquitin activator. In another embodiment a micro syringe is provided that injects the cell growth inhibiting ubiquitin activator directly into the adventitia. One specific embodiment includes a vascular stent having a cell growth inhibiting ubiquitin activator, specifically, hypothemycin. For example, to a solution of 250 μg of cell growth inhibiting ubiquitin activator in 27.56 mL of THF (THF), 251.6 mg of polycaprolactone was added forming a coating solution The cleaned, dried stainless steel stents were coated by either spraying or by dipping into the cell growth inhibiting ubiquitin activator/polymer medicament solution to achieve a final coating weight of approx. 10 μg to 1 mg.

IT **76958-67-3**, Hypothemycin
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. and devices comprising antiproliferative ubiquitin activator for treatment of vascular occlusions)

RN 76958-67-3 CAPLUS
CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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L3 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:964817 CAPLUS
DOCUMENT NUMBER: 141:410756
TITLE: Preparation of macrocyclic compounds for the treatment of inflammation and autoimmune disorders
INVENTOR(S): Chiba, Kenichi; Du, Hong; Eguchi, Yoshihito; Fujita, Masanori; Goto, Masaki; Gusovsky, Fabian; Harmange, Jean-Christophe; Inoue, Atsushi; Kawada, Megumi; Kawai, Takatoshi; Kawakami, Yoshiyuki; Kimura, Akifumi; Kotake, Makoto; Kuboi, Yoshikazu; Matsushima, Tomohiro; Mizui, Yoshiharu; Muramoto, Kenzo; Sakurai, Hideki; Shen, Yong-chun; Shirota, Hiroshi; Spyvee, Mark; Tanaka, Isao; Wang, John; Wood, Ray; Yamamoto, Satoshi; Yoneda, Naoki
PATENT ASSIGNEE(S): Japan
SOURCE: U.S. Pat. Appl. Publ., 299 pp., Cont.-in-part of Appl. No. PCT/US03/07377.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004224936	A1	20041111	US 2003-657910	20030909
WO 2003076424	A1	20030918	WO 2003-US7377	20030307

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,

KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-362883P P 20020308
US 2002-380711P P 20020514
WO 2003-US7377 A2 20030307

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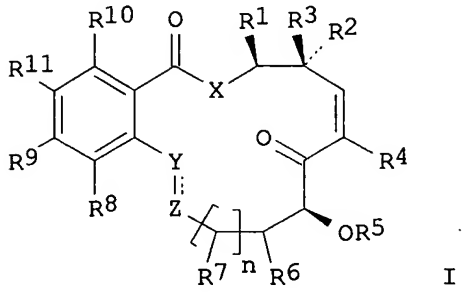

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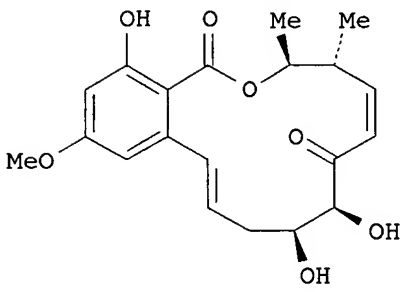


II

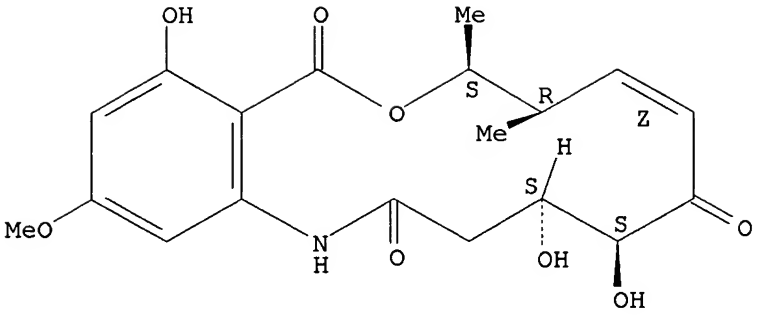
AB Macrocyclic compds. of formula I [R1 = H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, etc.; R2, R3 = H, halo, (substituted) OH, alkyl, aryl, etc.; R1R2, R1R3 = alkylene; R4 = H, halo; R5 = H, protecting group, prodrug; R6, R7, R11 = H, (substituted) OH; R8, R9 = H, halo, (substituted) OH, alkoxy, etc.; R10 = H, (substituted) OH, (substituted) NH2; n = 0-2; X = absent, O, NH, N-alkyl, CH2, S; Y, Z = CH, O, CO, NH, etc.] are prepared for the treatment of various disorders including inflammatory or autoimmune disorders, and disorders involving malignancy or increased angiogenesis. In certain embodiments, methods for the treatment of various disorders including inflammatory or autoimmune disorders comprise systemically (e.g., orally) administering to a subject in need thereof a therapeutically effective amount of a compound of formula I. Thus, II was prepared in several steps. Some of the compds. inhibited NF-κB with IC50 values < 10μM.

IT **603045-43-8P 791101-06-9P 791101-07-0P**
791101-08-1P 791101-09-2P 791101-10-5P
791807-02-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic compds. for the treatment of inflammatory or autoimmune disorders)

RN 603045-43-8 CAPLUS

CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione, 4,5,9,10-tetrahydro-4,5,13-trihydroxy-15-methoxy-9,10-dimethyl-, (4S,5S,7Z,9R,10S)- (9CI) (CA INDEX NAME)

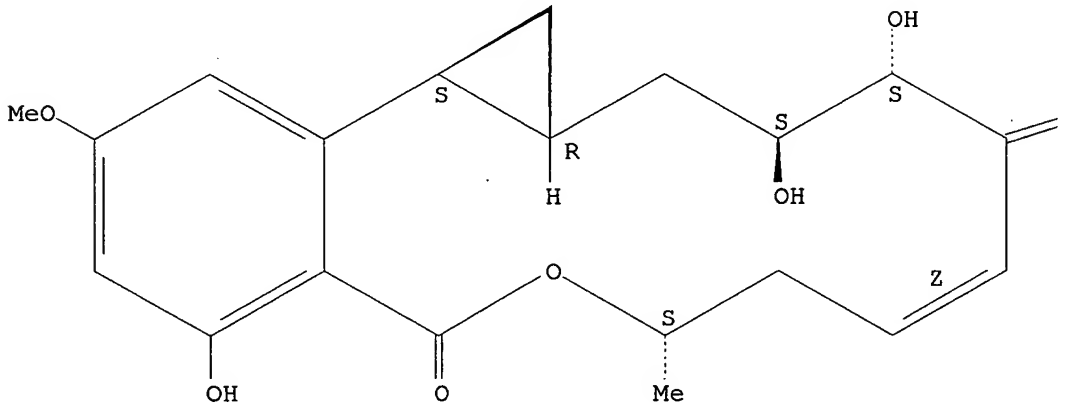
Absolute stereochemistry.
Double bond geometry as shown.



RN 791101-06-9 CAPLUS
CN Benzo[c]cycloprop[e]oxacyclotetradecin-5,11-dione, 7,8,12,13,14,14a,15,15a-octahydro-4,12,13-trihydroxy-2-methoxy-7-methyl-, (7S,9Z,12S,13S,14aR,15aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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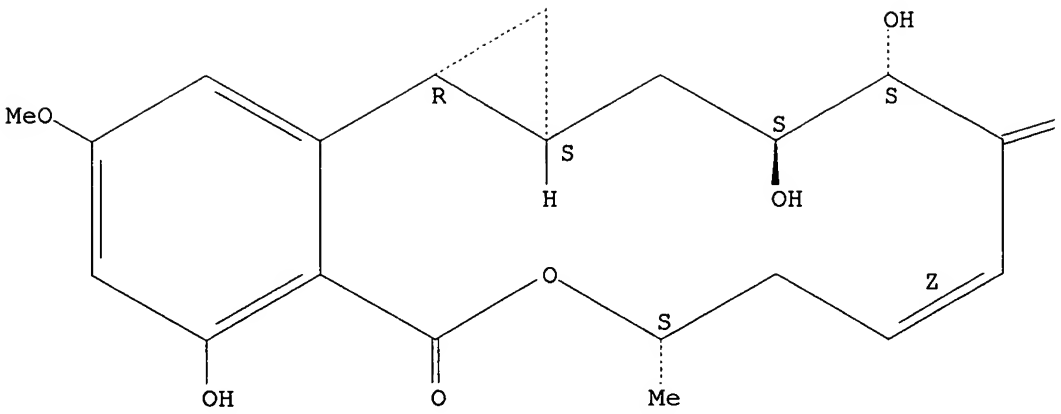
RN 791101-07-0 CAPLUS
CN Benzo[c]cycloprop[e]oxacyclotetradecin-5,11-dione, 7,8,12,13,14,14a,15,15a-octahydro-4,12,13-trihydroxy-2-methoxy-7-methyl-, (7S,9Z,12S,13S,14aS,15aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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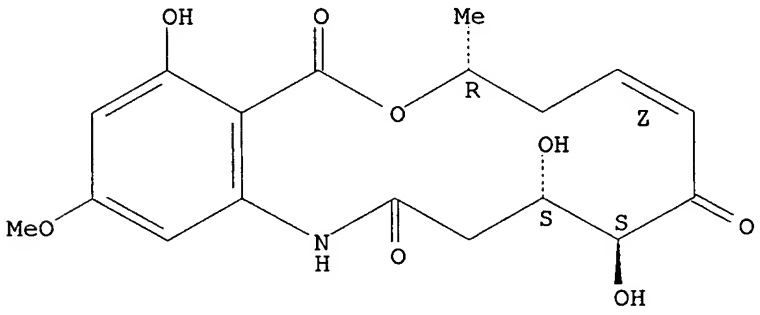
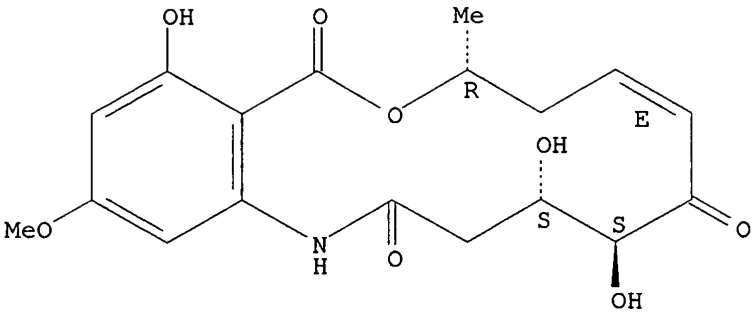
RN 791101-08-1 CAPLUS
CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione, 4,5,9,10-tetrahydro-4,5,13-trihydroxy-15-methoxy-10-methyl-, (4S,5S,7Z,10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



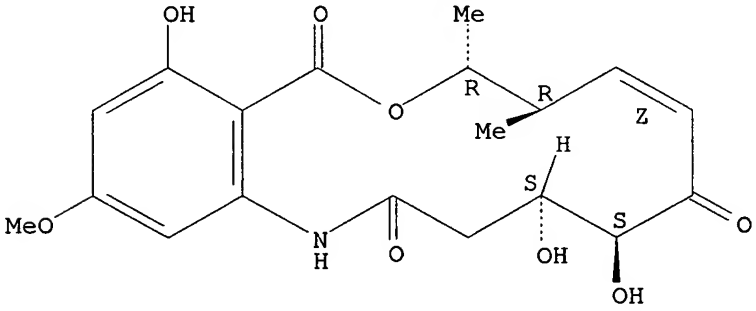
RN 791101-09-2 CAPLUS
CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione, 4,5,9,10-tetrahydro-4,5,13-trihydroxy-15-methoxy-10-methyl-, (4S,5S,7E,10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.



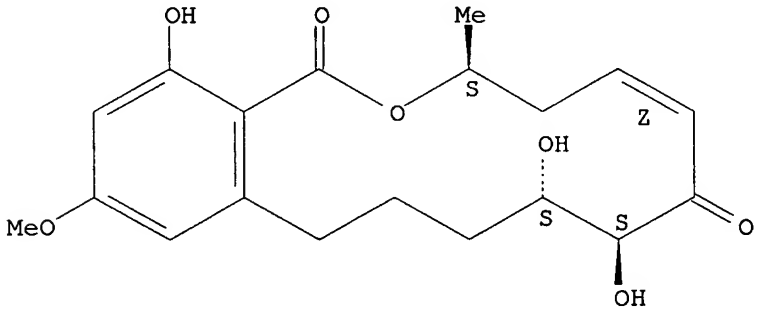
RN 791101-10-5 CAPLUS
CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione, 4,5,9,10-tetrahydro-4,5,13-trihydroxy-15-methoxy-9,10-dimethyl-, (4S,5S,7Z,9R,10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 791807-02-8 CAPLUS
CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (3S,5Z,8S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L3 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:42365 CAPLUS
DOCUMENT NUMBER: 140:213678
TITLE: Ketene acetal and spiroacetal constituents of the marine fungus Aigialus parvus BCC 5311
AUTHOR(S): Vongvilai, Pornrapee; Isaka, Masahiko; Kittakoop, Prasat; Srikitikulchai, Prasert; Kongsaeree,

Palangpon; Thebtaranonth, Yodhathai
CORPORATE SOURCE: Department of Chemistry, Faculty of Science, Mahidol University, Bangkok, 10400, Thailand
SOURCE: Journal of Natural Products (2004), 67(3), 457-460
CODEN: JNPRDF; ISSN: 0163-3864
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
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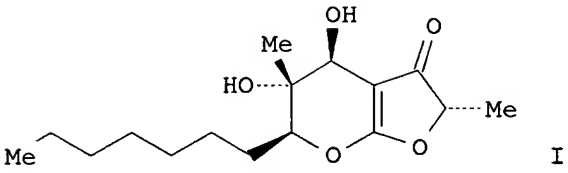

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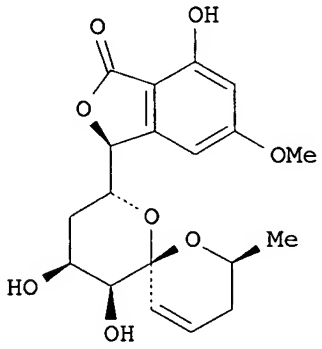


II

AB Aigialone (I) and aigialospirol (II), two structurally unique compds., were isolated from the mangrove fungus Aigialus parvus BCC 5311. The structure of I was elucidated by spectral anal., and its relative stereochem. was determined by X-ray crystallog. The stereochem. of II, elucidated by NMR spectral anal., suggested that this compound is possibly derived from hypothemycin, a metabolite previously isolated from this same fungus.

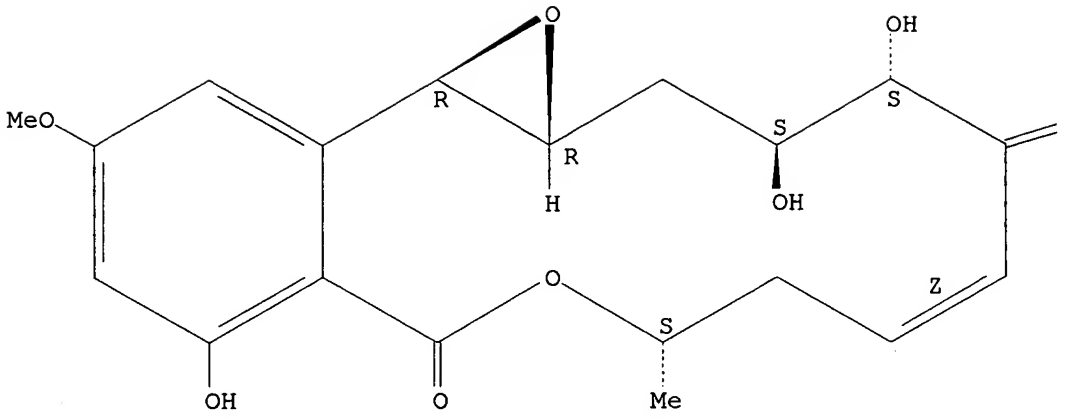
IT **76958-67-3**, Hypothemycin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(constituents of the marine fungus Aigialus parvus BCC 5311)

RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:41213 CAPLUS
DOCUMENT NUMBER: 140:105249
TITLE: Combination of mTOR inhibitor and a tyrosine kinase inhibitor for the treatment of neoplasms
INVENTOR(S): Neel, Benjamin G.; Mohi, Golam
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004644	A2	20040115	WO 2003-US20972	20030703
WO 2004004644	A3	20040506		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-394029P P 20020705
US 2002-412402P P 20020920

AB The invention features methods and compns. including an mTOR inhibitor and a tyrosine kinase inhibitor for reducing the proliferation of and

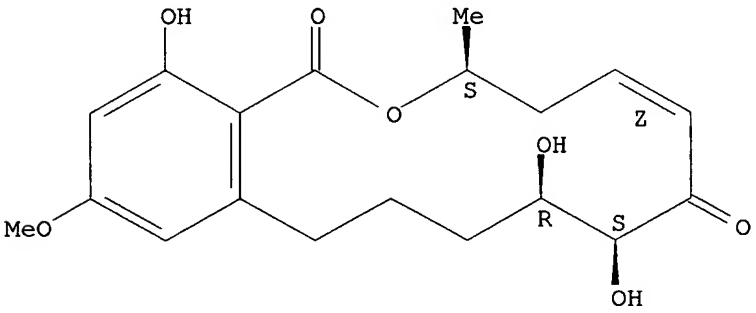
enhancing the apoptosis of neoplastic cells. The addition of an MEK inhibitor to this combination further enhances the effectiveness of this therapeutic method.

IT **219917-92-7**, L 783277
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(L 783277; combination of mTOR inhibitor and tyrosine kinase inhibitor for cancer therapy)

RN 219917-92-7 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (3R,5Z,8R,9S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.
Currently available stereo shown.



L3 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:737744 CAPLUS
DOCUMENT NUMBER: 139:261090
TITLE: Preparation of macrocyclic compounds for use in pharmaceutical and cosmetic compositions which regulate various genes involved in immune and inflammatory responses
INVENTOR(S): Boivin, Roch; Chiba, Kenichi; Davis, Heather A.; Diepitro, Lucian; Du, Hong; Eguchi, Yoshihito; Fujita, Masanori; Gilbert, Sandra; Goto, Masaki; Harmange, Jean Christophe; Inoue, Atsushi; Jiang, Yimin; Kawada, Megumi; Kawai, Takatoshi; Kawakami, Yoshiyuki; Kimura, Akifumi; Kotake, Makoto; Kuboi, Yoshikazu; Lemelin, Charles; Li, Xiang-yi; Matsushima, Tomohiro; Mizui, Yoshiharu; Sakurai, Hideki; Schiller, Shawn; Shen, Yongchun; Spyvee, Mark; Tanaka, Isao; Wang, Yuan; Yamamoto, Satoshi; Yoneda, Naoki; Kobayashi, Seiichi
PATENT ASSIGNEE(S): Eisai Co. Ltd., Japan; et al.
SOURCE: PCT Int. Appl., 438 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003076424	A1	20030918	WO 2003-US7377	20030307

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PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
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FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004224936 A1 20041111 US 2003-657910 20030909
PRIORITY APPLN. INFO.: US 2002-362883P P 20020308
US 2002-380711P P 20020514
WO 2003-US7377 A2 20030307

OTHER SOURCE(S): MARPAT 139:261090
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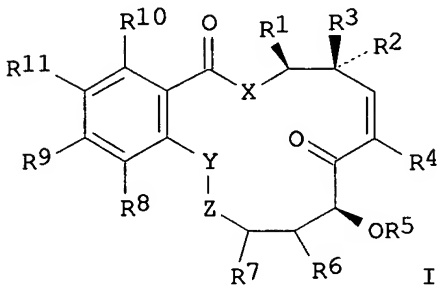

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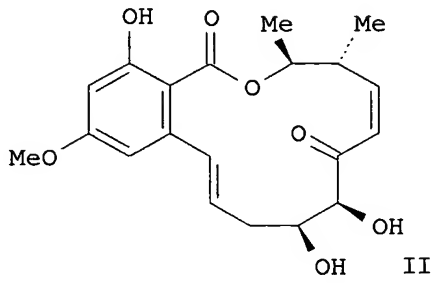

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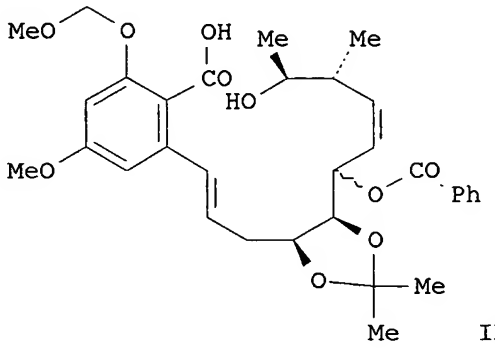


III

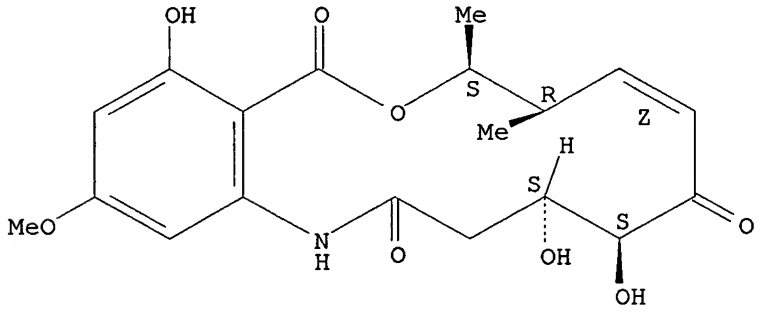
AB Macrocyclic lactones and lactams, such as I [R1 = H, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl; R2, R3 = H, OH, halogen, protected hydroxyl, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl; R1R2 or R1R3 = 3-8 membered alicyclic ring; R4 = H, halogen; R5 = H, hydroxyl protecting group, linked prodrug; R6, R7 = H, OH, protected hydroxyl; R8, R9, R10, R11 = H, OH, NH2, alkoxy, alkylamino, etc.; X = O, NH, S, CH2, etc.; R8R9 = fused ring, such as furan or imidazole; Y-Z = CH:CH, NHCO, etc.], were prepared for a variety of therapeutic and cosmetic uses, such as antitumor and anti-inflammatory agents and treatment of skin photodamage. These macrocycles are claimed for use as NF-κB, AP-1, protein kinase, cancer cell proliferation and solid tumor angiogenesis inhibitors and for use in the treatment of inflammation, cancer, psoriasis, skin photodamage, restenosis as stent coatings, rheumatoid arthritis, asthma, sepsis, inflammatory bowel disease, atopic dermatitis, Crohn's disease, autoimmune disorders and for treatment of gastrointestinal, esophageal, tracheal/bronchial, urethral and vascular obstructions wherein the lumen of a body passageway is expanded. Thus, macrocyclic lactone II, designated as ER 803064, was prepared via a multistep synthetic sequence with included a macrolactonization reaction of III to form the desired lactone ring. The

prepared macrocycles were assayed for their effect on TNF-α and β-actin placental alkaline phosphatase transcription using human acute monocytic leukemia cells.

IT **603045-43-8P**, NF 2306 **603959-48-4P 603959-63-3P**
603985-29-1P, NF 1535
RL: COS (Cosmetic use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic compds. for use in pharmaceutical and cosmetic compns. which regulate various genes involved in immune and inflammatory responses)

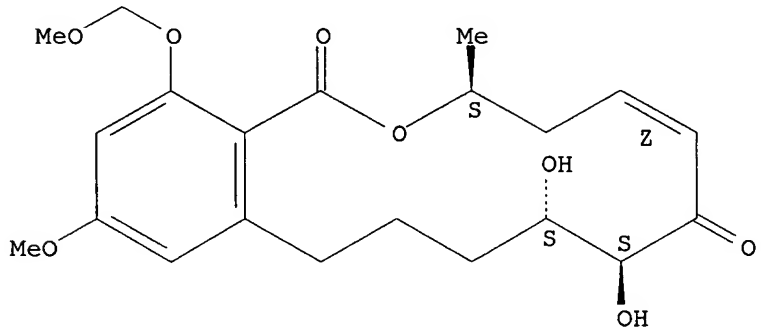
RN 603045-43-8 CAPLUS
CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione, 4,5,9,10-tetrahydro-4,5,13-trihydroxy-15-methoxy-9,10-dimethyl-, (4S,5S,7Z,9R,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



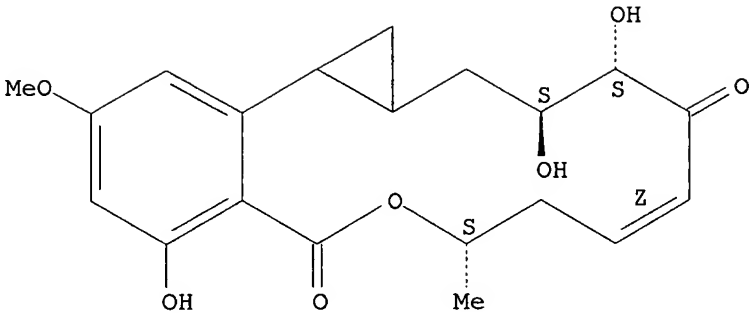
RN 603959-48-4 CAPLUS
CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9-dihydroxy-14-methoxy-16-(methoxymethoxy)-3-methyl-, (3S,5Z,8S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



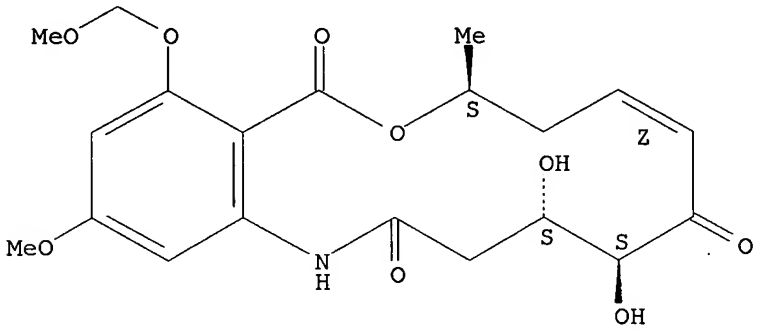
RN 603959-63-3 CAPLUS
CN Benzo[c]cycloprop[e]oxacyclotetradecin-5,11-dione, 7,8,12,13,14,14a,15,15a-octahydro-4,12,13-trihydroxy-2-methoxy-7-methyl-, (7S,9Z,12S,13S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



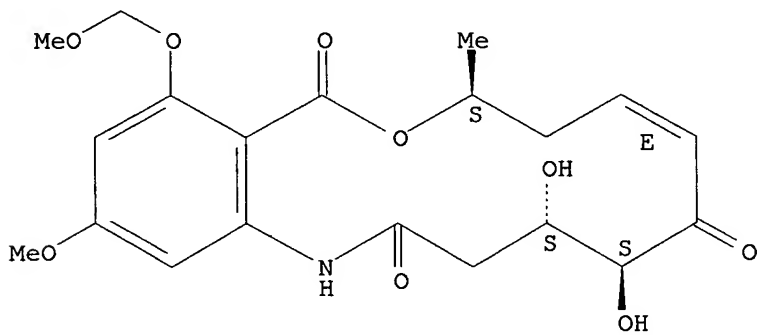
RN 603985-29-1 CAPLUS
CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione, 4,5,9,10-tetrahydro-4,5-dihydroxy-15-methoxy-13-(methoxymethoxy)-10-methyl-, (4S,5S,7Z,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



IT **603985-32-6P**, NF 1537
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of macrocyclic compds. for use in pharmaceutical and cosmetic compns. which regulate various genes involved in immune and inflammatory responses)
RN 603985-32-6 CAPLUS
CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione, 4,5,9,10-tetrahydro-4,5-dihydroxy-15-methoxy-13-(methoxymethoxy)-10-methyl-, (4S,5S,7E,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

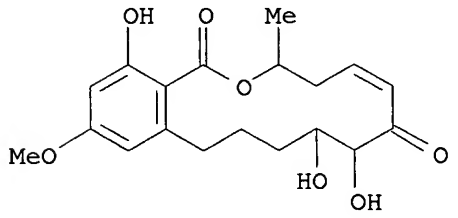
L3 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:465995 CAPLUS
DOCUMENT NUMBER: 137:28332
TITLE: Tak1 inhibitors
INVENTOR(S): Tsuchiya, Masayuki; Ohtomo, Toshihiko; Ono, Koichiro; Matsumoto, Masahiko; Ito, Tatsuya
PATENT ASSIGNEE(S): Chugai Seiyaku Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002048135	A1	20020620	WO 2001-JP10927	20011213
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2004292315	A2	20041021	JP 2000-379995	20001214
AU 2002022627	A5	20020624	AU 2002-22627	20011213
PRIORITY APPLN. INFO.:			JP 2000-379995 A	20001214
			WO 2001-JP10927 W	20011213

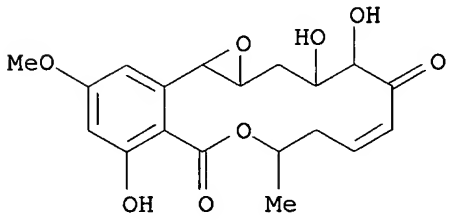
AB TAK1 inhibitors or TAK1 activation inhibitors containing as the active ingredient zearalenones having hydroxyl groups at both of the 8- and 9-positions; a method of inhibiting TAK1 or a method of inhibiting the activation of TAK1 by using as the active ingredient zearalenones having hydroxyl groups at both of the 8- and 9-positions; utilization of zearalenones having hydroxyl groups at both of the 8- and 9-positions for producing TAK1 inhibitors or TAK1 activation inhibitors; and kits for inhibiting TAK1 or kits for inhibiting the activation of TAK1 containing zearalenones having hydroxyl groups at both of the 8- and 9-position and a manual.

IT **219861-66-2 437611-54-6**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(zearalenones as Tak1 inhibitors for treatment of related diseases)

RN 219861-66-2 CAPLUS
CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl- (9CI) (CA INDEX NAME)

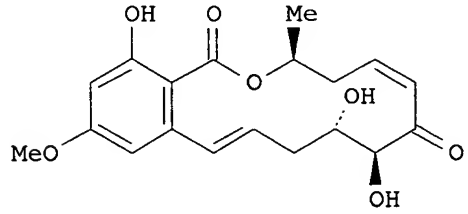


RN 437611-54-6 CAPLUS
CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:456594 CAPLUS
DOCUMENT NUMBER: 137:247530
TITLE: Convergent stereospecific synthesis of LL-Z1640-2 (or C292), hypothemycin and related macrolides. Part 2
AUTHOR(S): Selles, Patrice; Lett, Robert
CORPORATE SOURCE: Unite Mixte, CNRS-AVENTIS Pharma, Romainville, 93235, Fr.
SOURCE: Tetrahedron Letters (2002), 43(26), 4627-4631
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:247530
GI



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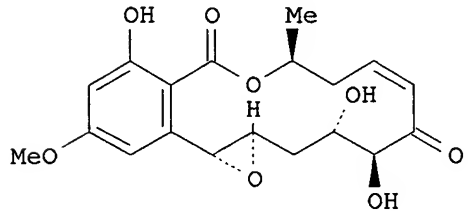


II

AB The total syntheses of C292 (or LL-Z1640-2, I) and hypothemycin (II) have been achieved. The 14-membered ring formation was achieved either via an intramol. Suzuki coupling or much more efficiently via a Mitsunobu macrolactonization. Reaction conditions were found to preserve the Z enone present in the targets. Selective epoxidn. of C292 (I) afforded hypothemycin (II).
IT **76958-67-3P**

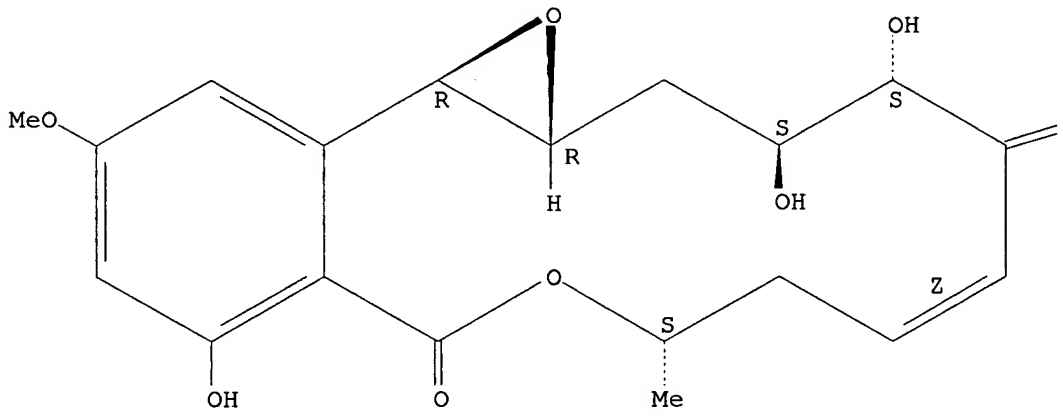
RL: SPN (Synthetic preparation); PREP (Preparation)
(convergent stereospecific synthesis of C292, hypothemycin and related macrolides)

RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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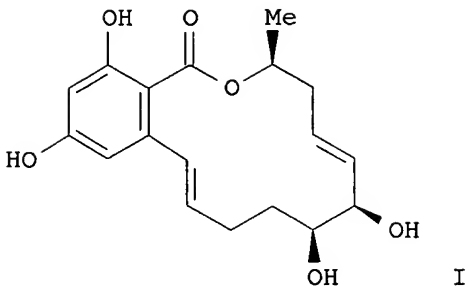
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:101776 CAPLUS
DOCUMENT NUMBER: 136:321761
TITLE: Aigialomycins A-E, new resorcylic macrolides from the marine mangrove fungus Aigialus parvus
AUTHOR(S): Isaka, Masahiko; Suyarnsestakorn, Chotika; Tanticharoen, Morakot; Kongsaeree, Palangpon; Thebtaranonth, Yodhathai
CORPORATE SOURCE: National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency (NSTDA), Bangkok, 10400, Thailand
SOURCE: Journal of Organic Chemistry (2002), 67(5), 1561-1566
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Aigialomycins A-E, new 14-membered resorcylic macrolides, were isolated, together with hypothemycin, from the mangrove fungus Aigialus parvus BCC 5311. Structures of these compds., including absolute configuration, were elucidated by spectroscopic methods, chemical conversions, and X-ray crystallog. anal. Hypothemycin and aigialomycin D (I) exhibited in vitro antimalarial activity with IC50 values of 2.2 and 6.6 μg/mL, resp., while other analogs were inactive. Cytotoxicities of these compds. were also evaluated.

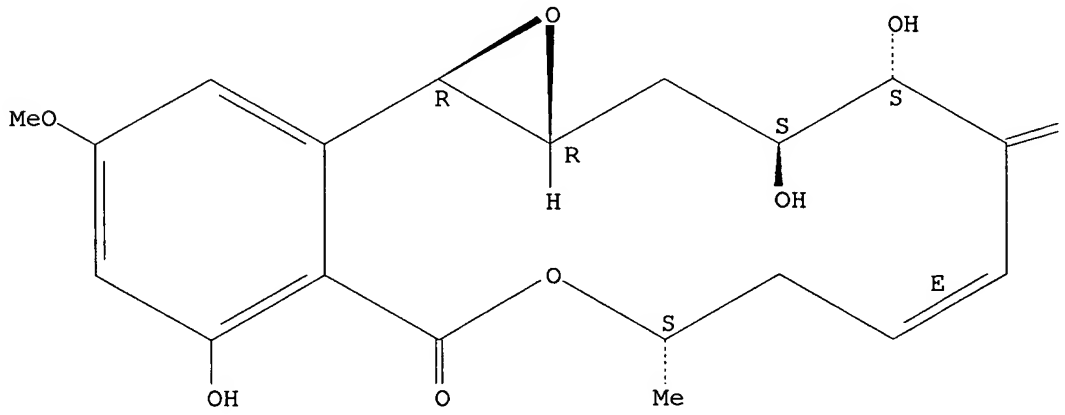
IT **412328-17-7P**, Aigialomycin A
RL: BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(aigialomycins A-E, new resorcylic macrolides from the marine mangrove fungus Aigialus parvus)

RN 412328-17-7 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6E,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as described by E or Z.

PAGE 1-A

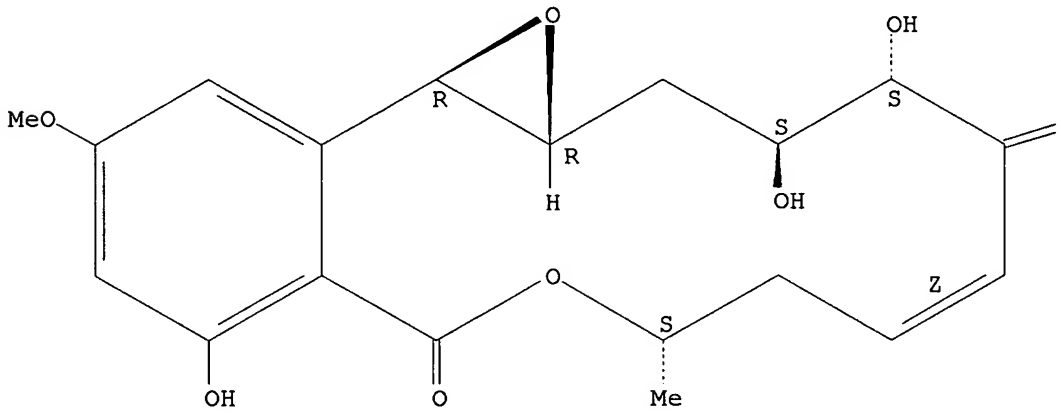


PAGE 1-B

IT **76958-67-3**, Hypothemycin
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(macrolides from the marine mangrove fungus Aigialus parvus)
RN 76958-67-3 CAPLUS
CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:380438 CAPLUS
DOCUMENT NUMBER: 135:24657
TITLE: Selective cellular targeting: multifunctional delivery vehicles
INVENTOR(S): Glazier, Arnold
PATENT ASSIGNEE(S): Drug Innovation & Design, Inc., USA
SOURCE: PCT Int. Appl., 981 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001036003	A2	20010525	WO 2000-US31262	20001114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,				

LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2391534	AA	20010525	CA 2000-2391534	20001114
AU 2001016075	A5	20010530	AU 2001-16075	20001114
EP 1255567	A1	20021113	EP 2000-978631	20001114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003138432	A1	20030724	US 2000-738625	20001215

PRIORITY APPLN. INFO.:

US 1999-165485P	P	19991115
US 2000-239478P	P	20001011
US 2000-241937P	P	20001020
WO 2000-US31262	W	20001114
US 2000-712465	B1	20001115

AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

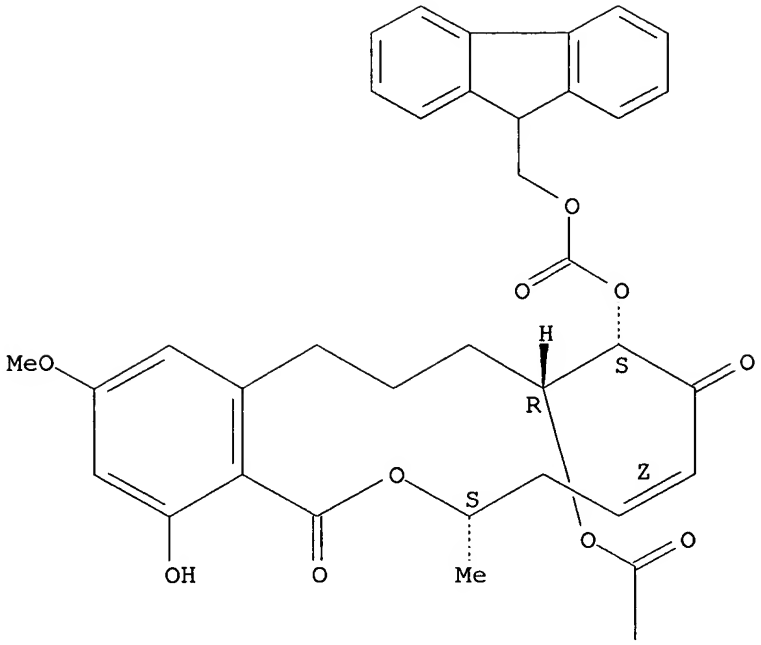
IT **341552-13-4P**
RL: PNU (Preparation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(multifunctional delivery vehicles for selective cellular targeting of drugs)

RN 341552-13-4 CAPLUS

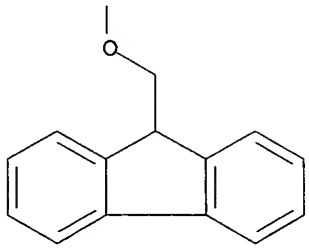
CN Carbonic acid, (3S,5Z,8S,9R)-3,4,7,8,9,10,11,12-octahydro-16-hydroxy-14-methoxy-3-methyl-1,7-dioxo-1H-2-benzoxacyclotetradecin-8,9-diyl bis(9H-fluoren-9-ylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 2-A



L3 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:820950 CAPLUS
DOCUMENT NUMBER: 134:360851
TITLE: Chemical inducers for morphological reversion of oncogenically transformed NIH3T3 cells
AUTHOR(S): Sonoda, Hikaru; Omi, Kazuo
CORPORATE SOURCE: Diagnostics Science Division, Shionogi Research Laboratories, Shionogi and Co., Ltd., Osaka, 553-0002, Japan
SOURCE: Shionogi Kenkyusho Nenpo (2000), 50, 1-18
CODEN: SKNEA7; ISSN: 0559-8680
PUBLISHER: Shionogi Seiyaku K.K. Chuo Kenkyusho
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 96 refs. In the course of screening for antitumor drugs by using oncogene-transformed NIH3T3 cells, several compds., including trichostatin A, trapoxins, depudecin, oxamflatin, hypothemycin, geldanamycin and radicicol, have been found to cause reversion of the spindled morphol. of the transformed cells to the flat type. Mechanistic studies on these compds. have revealed that some share modes of action on

the inhibition of cellular transformation. Trichostatin A, trapoxins, depudecin and oxamflatin inhibit histone deacetylase activity. Hypothemycin, which has several structural analogs of natural origin, can inhibit MEK [not defined] family kinases. Geldanamycin and radicicol can bind to the mol. chaperone Hsp90 and accelerate the degradation of its partner proteins. This article gives an overview of the antitransformation activities of these compds. and discusses how these inhibitors of histone deacetylase, MEK family kinases and Hsp90 protein chaperone can suppress the transformation triggered by oncogenes such as v-ras and v-raf.

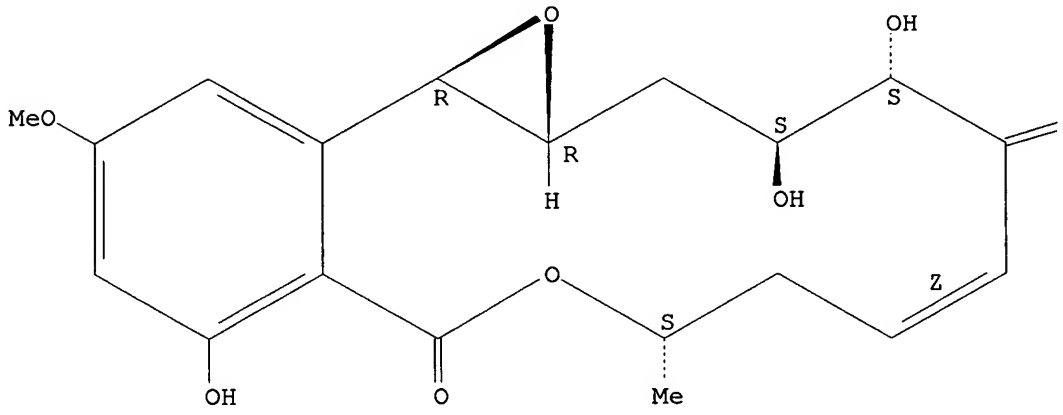
IT **76958-67-3**, Hypothemycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(morphol. reversion of oncogenically transformed NIH3T3 cells by)

RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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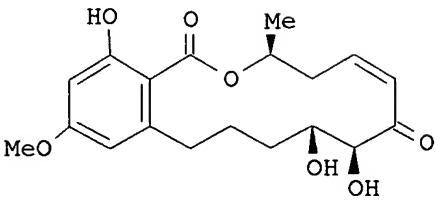
REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:17527 CAPLUS
DOCUMENT NUMBER: 132:191536
TITLE: Resorcylic acid lactones: naturally occurring potent and selective inhibitors of MEK
AUTHOR(S): Zhao, Annie; Lee, Seok H.; Mojena, Marina; Jenkins, Rosalind G.; Patrick, Denis R.; Huber, Hans E.; Goetz, Michael A.; Hensens, Otto D.; Zink, Deborah L.; Vilella, Dolores; Dombrowski, Anne W.; Lingham, Russell B.; Huang, Leeyuan
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA

SOURCE: Journal of Antibiotics (1999), 52(12), 1086-1094
CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER: Japan Antibiotics Research Association
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

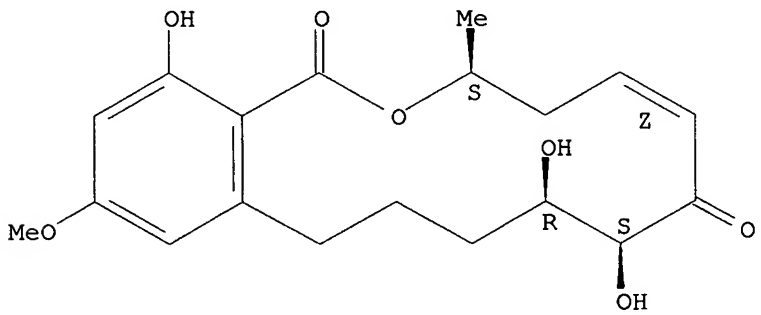
AB A resorcylic acid lactone, L-783,277 (I), isolated from a Phoma sp. (ATCC 74403) which came from the fruitbody of Helvella acetabulum, is a potent and specific inhibitor of MEK (Map kinase kinase). L-783,277 inhibits MEK with an IC50 value of 4 nM. It weakly inhibits Lck and is inactive against Raf, PKA and PKC. L-783,277 is an irreversible inhibitor of MEK and is competitive with respect to ATP. L-783,290, the trans-isomer of L-783,277, was isolated from the same culture and evaluated together with several semi-synthetic resorcylic acid lactone analogs. A preliminary structure-activity relationship is presented. Several independent cell-based assays have been carried out to study the biol. activities of these resorcylic acid lactone compds. and a brief result summary from these studies is presented.

IT **219917-92-7P**, L 783277
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); RCT (Reactant); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); RACT (Reactant or reagent)
(isolation, structure and bioactivity of L-783,277, a resorcylic acid lactone isolated from a Phoma sp.)

RN 219917-92-7 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (3R,5Z,8R,9S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.
Currently available stereo shown.



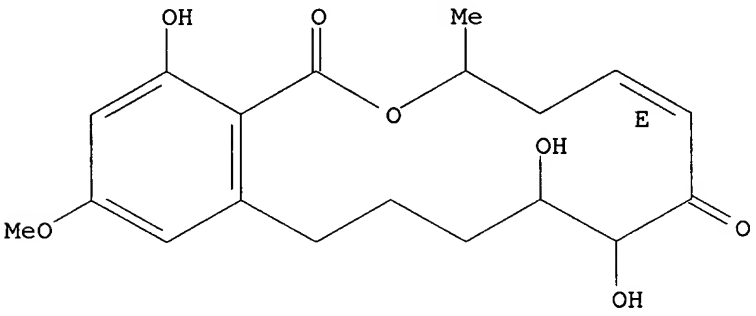
IT **219917-93-8P**, L 783290
RL: BAC (Biological activity or effector, except adverse); BOC (Biological

occurrence); BSU (Biological study, unclassified); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(isolation, structure and bioactivity of L-783,277, a resorcylic acid lactone isolated from a Phoma sp.)

RN 219917-93-8 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (5E)- (9CI) (CA INDEX NAME)

Double bond geometry as described by E or Z.
Currently available stereo shown.



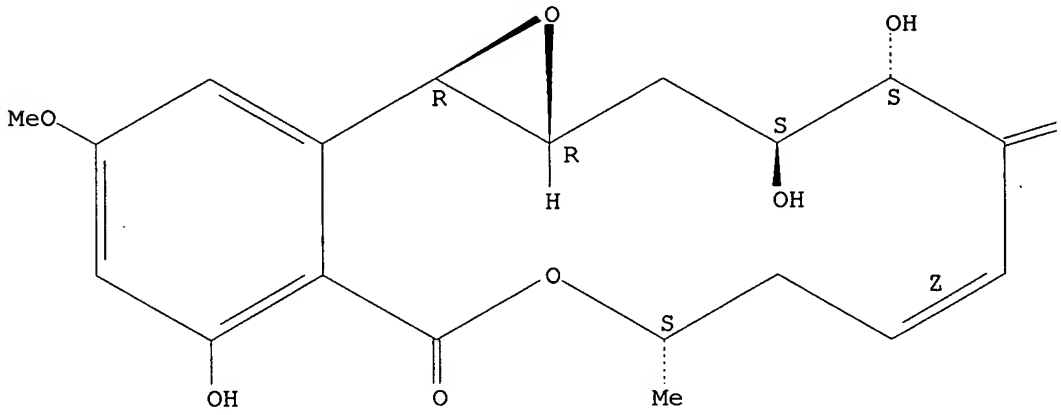
IT **76958-67-3**, Hypothemycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(isolation, structure and bioactivity of L-783,277, a resorcylic acid lactone isolated from a Phoma sp.)

RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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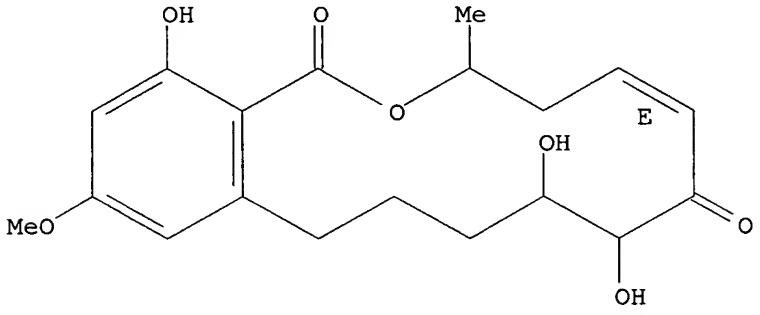
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:17526 CAPLUS
DOCUMENT NUMBER: 132:179619
TITLE: Production of a family of kinase-inhibiting lactones from fungal fermentations
AUTHOR(S): Dombrowski, Anne; Jenkins, Rosalind; Raghoobar, Susan; Bills, Gerald; Polishook, Jon; Pelaez, Fernando; Burgess, Bruce; Zhao, Annie; Huang, Leeyuan; Zhang, Yan; Goetz, Michael
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Antibiotics (1999), 52(12), 1077-1088
CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER: Japan Antibiotics Research Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB During the course of screening for natural products from fungi, exts. of several cultures were found to make a family of related resorcylic acid lactone compds., which are potent inhibitors of MEK kinase. Comparative and empirical studies of fermentation conditions improved the titers of the compds. of interest. Striking changes in the ratios and amts. of the major and minor compds. in some cases were achieved by manipulations of media composition

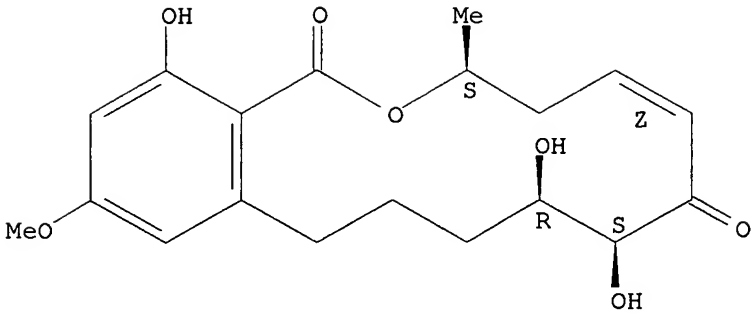
IT **219917-93-8P**
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(L 783290; production of a family of kinase-inhibiting lactones from fungal fermns.)
RN 219917-93-8 CAPLUS
CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (5E)- (9CI) (CA INDEX NAME)

Double bond geometry as described by E or Z.
Currently available stereo shown.



IT **219917-92-7P**, L 783277
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(production of a family of kinase-inhibiting lactones from fungal fermns.)
RN 219917-92-7 CAPLUS
CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (3R,5Z,8R,9S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.
Currently available stereo shown.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:812900 CAPLUS
DOCUMENT NUMBER: 132:117243
TITLE: Antitumor efficacy of hypothemycin, A new ras-signaling inhibitor
AUTHOR(S): Tanaka, Hidekazu; Nishida, Kazuyo; Sugita, Kenji; Yoshioka, Takayuki
CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi and Co., Ltd., Osaka, 553-0002, Japan
SOURCE: Japanese Journal of Cancer Research (1999), 90(10), 1139-1145
CODEN: JJCREP; ISSN: 0910-5050
PUBLISHER: Japanese Cancer Association
DOCUMENT TYPE: Journal
LANGUAGE: English

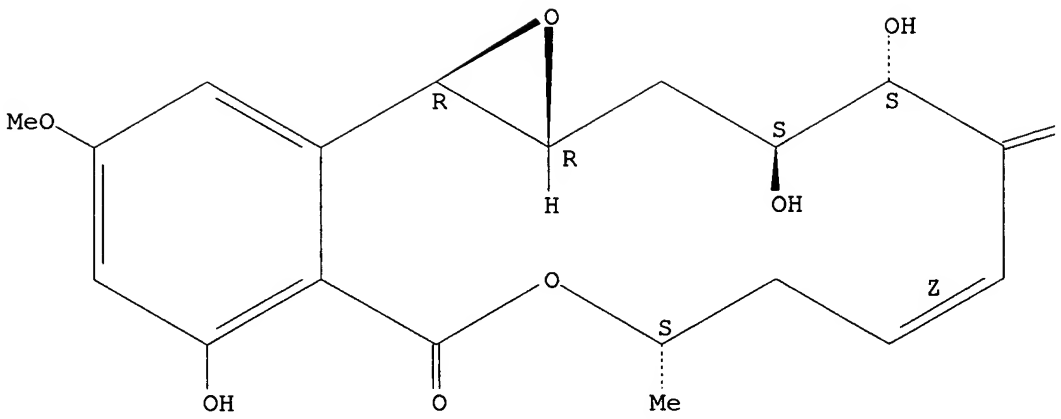
AB We have devised a new drug screening assay to discover anti-cancer drugs which inhibit Ras-mediated cellular signals, by utilizing a Ras-responsive element (RRE)-driven reporter gene system. We found that hypothemycin, an anti-bacterial, reduces RRE-dependent transcription. Treatment of tumor cells with hypothemycin resulted in reduced expression of Ras-inducible genes, including MMP (matrix metalloproteinase)-1, MMP-9, transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF), but not that of the constitutively expressed gene, MMP-2. The results of zymog. demonstrated that hypothemycin reduced the production of MMP-9 and MMP-3, another Ras-inducible MMP, in the culture medium. Hypothemycin selectively inhibits anchorage-independent growth of Ras-transformed cells in comparison with anchorage-dependent growth. These findings suggest that hypothemycin inhibits Ras-mediated cellular signaling. Daily treatment of tumor-bearing mice with hypothemycin resulted in significant inhibition of tumor growth. Since MMP-1, MMP-3 and MMP-9 play important roles in tumor invasion and TGF-β and VEGF are involved in tumor angiogenesis, hypothemycin is considered to be an example of a new class of antitumor drugs, whose antitumor efficacy can be at least partly attributed to inhibition of Ras-inducible genes.

IT **76958-67-3**, Hypothemycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor efficacy of hypothemycin, a new ras-signaling inhibitor)

RN 76958-67-3 CAPLUS
CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

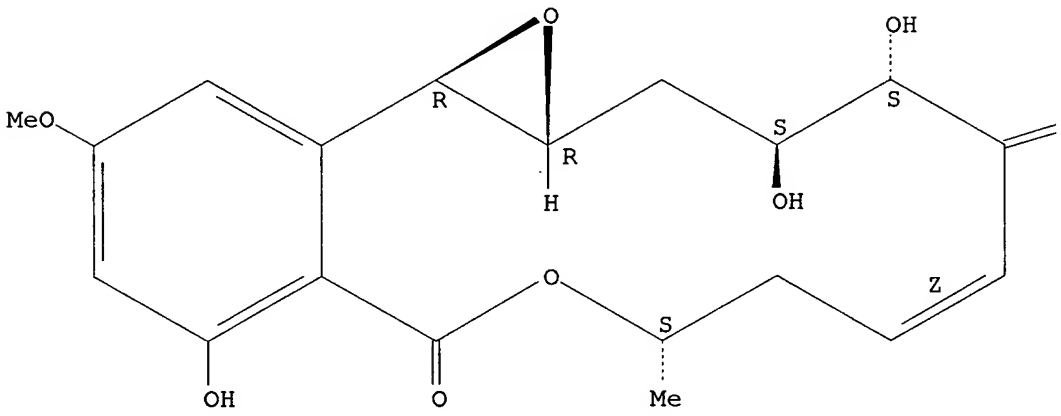
L3 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:806935 CAPLUS
DOCUMENT NUMBER: 132:132003
TITLE: Hypothemycin inhibits the proliferative response and modulates the production of cytokines during T cell activation
AUTHOR(S): Camacho, R.; Staruch, M. J.; DaSilva, C.; Koprak, S.; Sewell, T.; Salituro, G.; Dumont, F. J.
CORPORATE SOURCE: Rm. 80W107, Department of Immunology and Rheumatology, Merck Research Laboratories, Rahway, NJ, USA
SOURCE: Immunopharmacology (1999), 44(3), 255-265
CODEN: IMMUDP; ISSN: 0162-3109
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hypothemycin, a resorcylic acid lactone antibiotic, was identified as active in a screen for inhibitors of T cell activation. It was found to inhibit the proliferation of mouse and human T cells stimulated with anti-CD3 mAb+PMA and of human PBMC stimulated with anti-CD3 mAb alone. This inhibition was partially reversed by exogenous IL-2 indicating that it is not due to non-specific toxicity. Hypothemycin potently suppressed the production of IL-2 (IC50: 9 nM) but affected IL-2-induced proliferation to a lesser extent (IC50: 194 nM). Hypothemycin also inhibited IL-6, IL-10, IFN-γ and TNF-α production By contrast, it markedly enhanced the production of IL-4, IL-5 and IL-13. These effects were seen both at the mRNA and protein secretion levels. Anal. of the effect of hypothemycin on CD69 induction suggested that it disrupts calcineurin-independent rather than calcineurin-dependent signaling. Furthermore, hypothemycin was able to inhibit the phosphorylation of ERK1/2 induced by PMA treatment of T cells. Therefore, hypothemycin represents an inhibitor of T cell activation with a novel mode of action and unique modulatory activity on cytokine production

IT **76958-67-3**, Hypothemycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(hypothemycin inhibition of proliferative response and modulation of cytokine production during T cell activation)
RN 76958-67-3 CAPLUS
CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:428696 CAPLUS
DOCUMENT NUMBER: 131:193819
TITLE: Suppression of oncogenic transformation by hypothemycin associated with accelerated cyclin D1 degradation through ubiquitin-proteasome pathway
AUTHOR(S): Sonoda, Hikaru; Omi, Kazuo; Hojo, Kanji; Nishida, Kazuyo; Omura, Satoshi; Sugita, Kenji
CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, 553-0002, Japan
SOURCE: Life Sciences (1999), 65(4), 381-394
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hypothemycin was originally isolated as an antifungal metabolite of Hypomyces trichothecoides. Here we report that treatment on v-K-ras-transformed NIH3T3 cells (DT cells) with hypothemycin caused drastic decrease in amount of cyclin D1 protein with concomitant

prolongation of G1 phase in their cell cycle. Anal. using hypothemycin-resistant mutant of Schizosaccharomyces pombe (S. pombe) was carried out to show that S. pombe rhp6+ (homolog of Saccharomyces cerevisiae RAD6) and mammalian ubiquitin-conjugating enzyme 2 (ubc2) are the targets of hypothemycin or its downstream mols. in ubiquitin-conjugation process. Furthermore, in the presence of lactacystin, a specific inhibitor for proteasome, hypothemycin greatly enhanced the accumulation of multi-ubiquitinated form of cyclin D1 in DT cells. Therefore, it is indicated that hypothemycin facilitates ubiquitinating process of cyclin D1. In terms of malignant phenotype, hypothemycin inhibited anchorage-independent growth and reverted the morphol. of DT cells. On the contrary, their morphol. still remained transformed in the addnl. presence of lactacystin. Our results suggest that cyclin D1 is a key mol. working downstream in ras-signaling and that the transformation can be inhibited by the compound which can activate ubiquitin-proteasome pathway including degradation of cyclin D1.

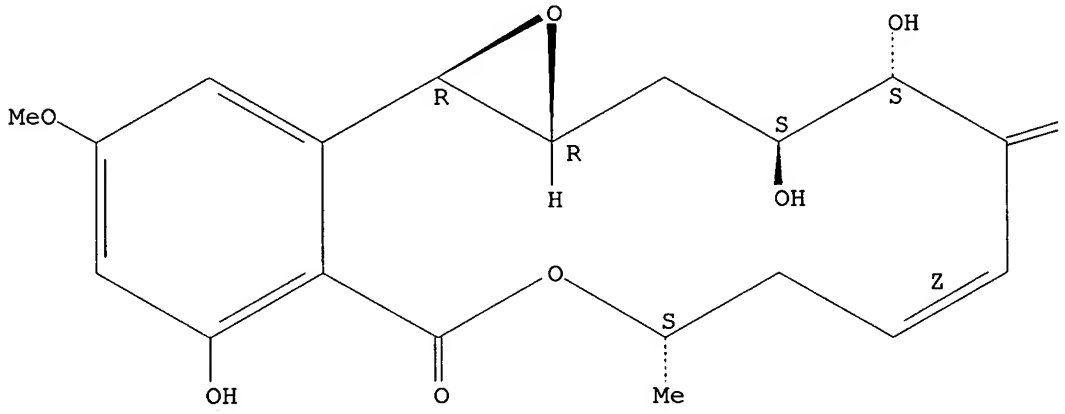
IT **76958-67-3,** Hypothemycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(suppression of oncogenic transformation by hypothemycin associated with accelerated cyclin D1 degradation through ubiquitin-proteasome pathway)

RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:59266 CAPLUS

DOCUMENT NUMBER: 130:119613
TITLE: MAPK/Erk kinase (MEK)-inhibiting lactones, production thereof from Phoma, and therapeutic use
INVENTOR(S): Bills, Gerald F.; Diez, Maria Teresa; Dombrowski, Anne W.; Falconi, Nicole D.; Goetz, Michael A.; Heimbrook, David C.; Hensens, Otto D.; Huang, Leeyuan; Huber, Hans E.; Jenkins, Rosalind G.; Kendall, Richard L.; Lee, Seok H.; Mojena, Marina; Oliff, Allen I.; Patrick, Denis R.; Pelaez, Fernando; Thomas, Kenneth A., Jr.; Vilella, Dolores; Zhao, Annie Z.; Zink, Deborah L.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Brit. UK Pat. Appl., 30 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
GB 2323845	A1	19981007	GB 1998-6929		19980331
PRIORITY APPLN. INFO.:			US 1997-42875P	P	19970331
			GB 1997-9292	A	19970507

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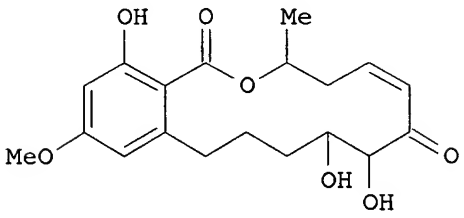


I

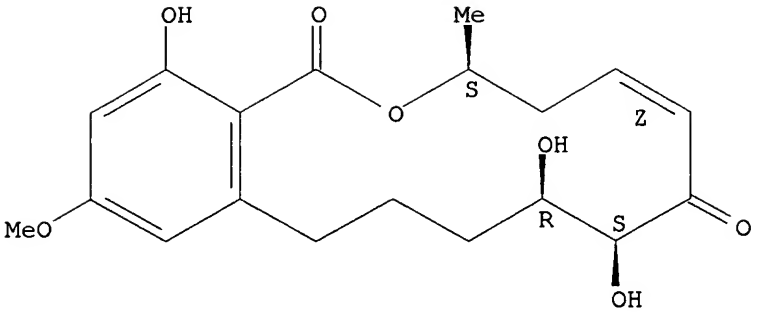
AB Compds. I are disclosed. I can be used for treating cancer and ocular disease, e.g. diabetic retinopathy, or other diseases where neoangiogenesis is implicated. Also disclosed is a culture of Phoma sp. which produces I, as well as a process for production of I.

IT **219917-92-7P 219917-93-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(MEK-inhibiting lactones, production from Phoma, and therapeutic use)

RN 219917-92-7 CAPLUS

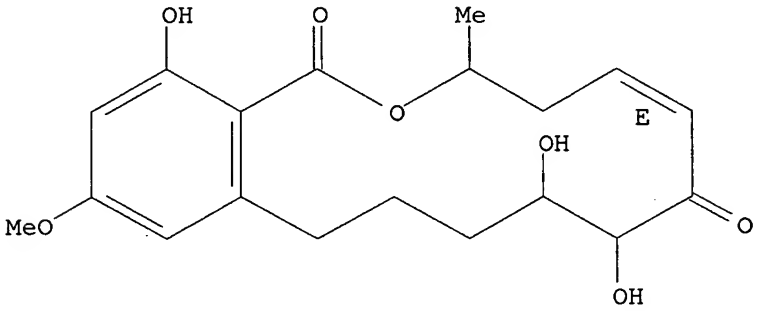
CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (3R,5Z,8R,9S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.
Currently available stereo shown.

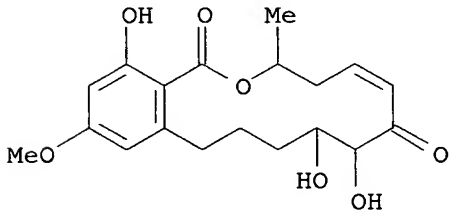


RN 219917-93-8 CAPLUS
CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (5E)- (9CI) (CA INDEX NAME)

Double bond geometry as described by E or Z.
Currently available stereo shown.

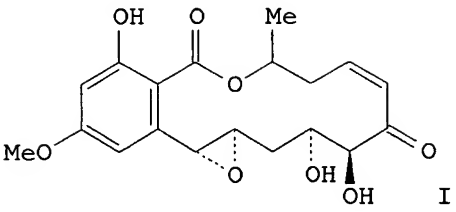


IT **219861-66-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MEK-inhibiting lactones, production from Phoma, and therapeutic use)
RN 219861-66-2 CAPLUS
CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl- (9CI) (CA INDEX NAME)

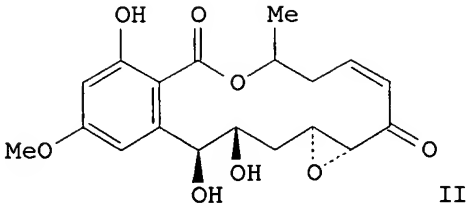


L3 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:495188 CAPLUS
DOCUMENT NUMBER: 119:95188
TITLE: Revised structure and stereochemistry of hypothemycin
AUTHOR(S): Agatsuma, Tsutomu; Takahashi, Akira; Kabuto, Chizuko; Nozoe, Shigeo
CORPORATE SOURCE: Fac. Pharm. Sci., Tohoku Univ., Sendai, 980, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1993), 41(2),

373-5
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II

AB A cytotoxic 14-membered resorcylic macrolide, isolated from Coriolus versicolor (L.: FR.) QUEL., was found to be identical with hypothemycin, previously isolated from Hypomyces trichothecoides. Based on NMR and x-ray crystal data the structure of hypothemycin has been elucidated to be I rather than the originally proposed II.

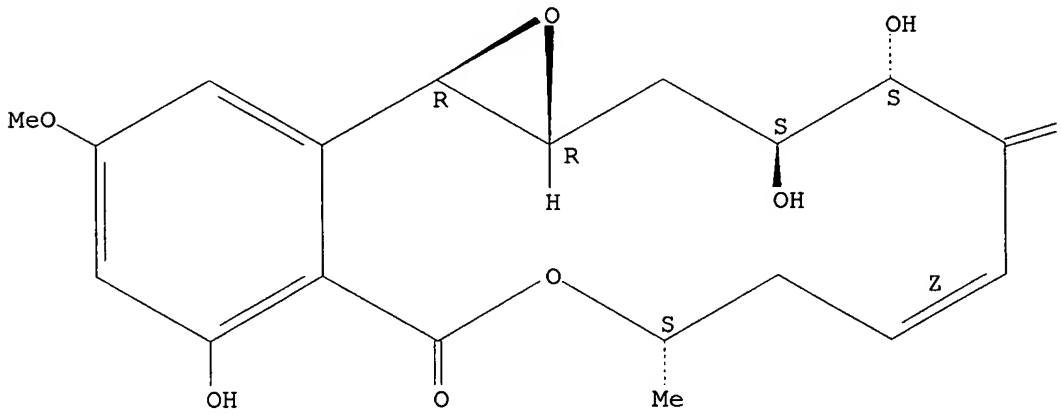
IT **76958-67-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(crystal structure, mol. structure, and absolute configuration of)

RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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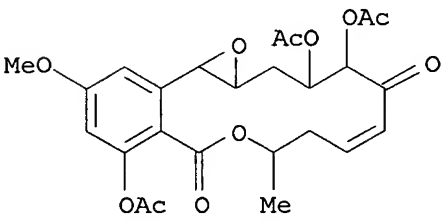
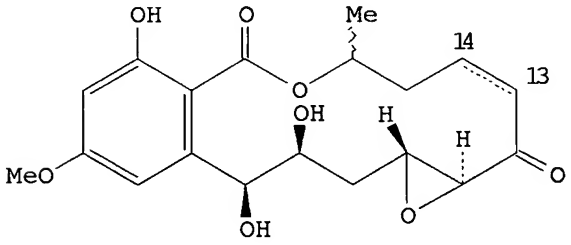
IT **149270-54-2P**, Hypothemycin triacetate
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 149270-54-2 CAPLUS
CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
3,4,12-tris(acetyloxy)-1a,8,9,15b-tetrahydro-14-methoxy-9-methyl-,
[1aR-(1aR*,3S*,4S*,6Z,9S*,15bR*)]- (9CI) (CA INDEX NAME)



L3 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1982:31271 CAPLUS
DOCUMENT NUMBER: 96:31271
TITLE: Metabolites of pyrenomycetes. XIV. Structure and partial stereochemistry of the antibiotic macrolides hypothemycin and dihydrohypothemycin
AUTHOR(S): Nair, M. S. R.; Carey, S. T.; James, J. C.
CORPORATE SOURCE: Osborn Lab. Mar. Sci., New York Aquarium, Brooklyn, NY, 11224, USA
SOURCE: Tetrahedron (1981), 37(14), 2445-9
CODEN: TETRAB; ISSN: 0040-4020
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

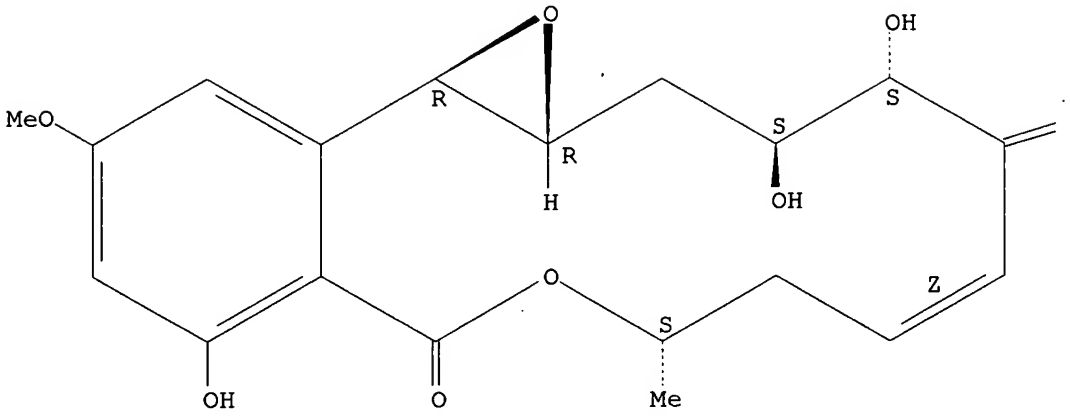


I, 13,14-unsatd.
II, 13,14-satd.

AB The structures of hypothemycin (I) and dihydrohypothemycin (II), which were isolated from the fungus Hypomyces trichothecoides, were determined by spectral anal. and chemical degradation The configurations of the macrolides were determined by NMR anal., particularly of the 2-dimensional J 1H spectra. I and II were active against Tetrahymena furgasoni, Ustilago maydis, and Botrytis allii.
IT **76958-67-3**
RL: BIOL (Biological study)
(from Hypomyces trichothecoides, structure and configuration of)
RN 76958-67-3 CAPLUS
CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-,
(1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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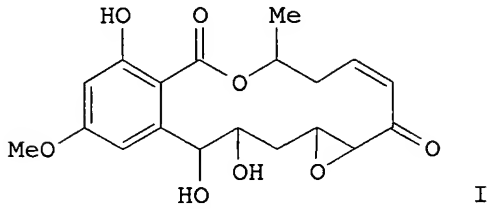
L3 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	1981:117417 CAPLUS
DOCUMENT NUMBER:	94:117417
TITLE:	Metabolites of pyrenomycetes. XIII. Structure of (+)-hypothemycin, an antibiotic macrolide from Hypomyces trichothecoides
AUTHOR(S):	Nair, M. S. R.; Carey, Susan T.
CORPORATE SOURCE:	New York Bot. Garden, Bronx, NY, 10458, USA
SOURCE:	Tetrahedron Letters (1980), 21(21), 2011-12 CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE:	Journal
LANGUAGE:	English

GI



I

AB On chemical evidence and spectroscopic data, the structure I was assigned to (+)-hypothemycin, a macrolide antibiotic metabolite from H. tricothecoides, which was active against Tetrahymena furgasoni (LD50 1 ppm), and to a lesser extent against Ustilago maydis.

IT **76958-67-3**
RL: BIOL (Biological study)

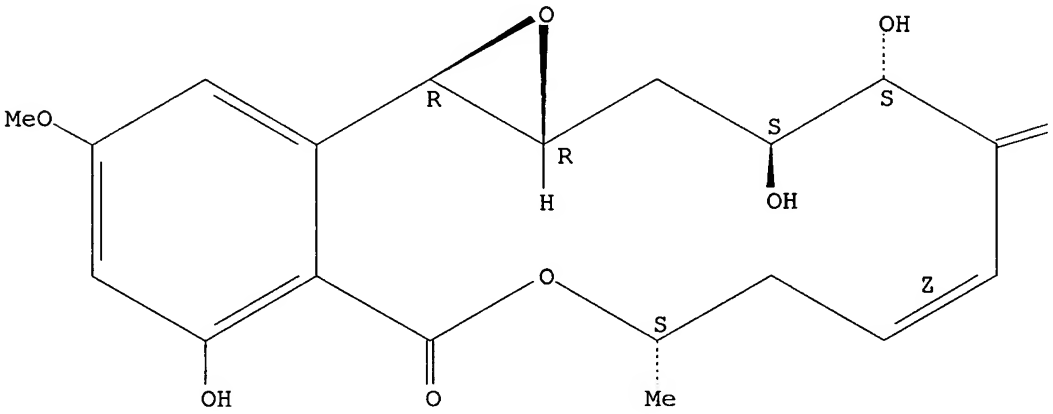
(from Hypomyces tricothecoides, structure of)

RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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